Applicants note that the terms "oncogenic," "tumorigenic," and "immortalizing" proteins represent synonyms. As noted in the specification, applicants' novel promoter sequences can direct neuron-specific expression of these proteins "to mimic tumorigenesis." Specification, page 6, lines 12-14. Accordingly, claims 40, 41, and 59 have also been amended to recite that the oncogenic protein is expressed "at a level sufficient to induce tumor formation in said neurons." The remaining amendments are discussed further below.

This Amendment does not introduce any new matter into the specification.

Drawings

Applicants submit new Formal Drawings with this Amendment and Response.

Enablement Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of clams 53 and 54 under 35 U.S.C. § 112, first paragraph, was withdrawn. However the rejection of claims 40-47, 51-52, and 55-58 under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled was maintained. In addition, newly added claims 59-62 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that does not enable one of skill in the art to which it pertains to make and/or use the invention. (Paper No. 20, page 3.) Applicants respectfully traverse this rejection.

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The Office has acknowledged that the specification enables one of skill in the art to make the claimed transgenic mice. (Paper No. Paper No. 12, page 2.) Thus, "[t]he issue is not the ability to create a transgenic mouse but rather whether the specification has taught a use for such a transgenic mouse in the absence of a recited phenotype." (*Id.*) In addition, "the Examiner acknowledges that the claimed invention could be used for tissue-specific tumor formation, particularly in neurons, or to create cell lines if the claimed transgenic mice were enabled as claimed." (Paper No. 20, page 8.) According to the Office:

> The main issue is that the evidence of record has not taught the creation of any of the claimed transgenic mice expressing oncogenic, tumorigenic, or immortalizing proteins, which exhibit a phenotype. Further as explained above the art of transgenics is unpredictable with regard to transgene expression and a resulting phenotype. As such, it cannot be predicted that expression of any oncogenic, tumorigenic, or immortalizing proteins as claimed would result in tumor formation. The Examiner agrees that tumor formation is a phenotype. However the evidence of record has not demonstrated that this aspect of transgenesis, tissue-specific tumor formation, is predictable.

Id.

The Office's real concern, therefore, appears to be the predictability of tumor formation in transgenic mice expressing an oncogene under the control of a tissue-specific promoter, and in particular, a promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor, as claimed. The Office relies on general teachings pertaining to the art of transgenic mice and contends that the phenotype resulting from the expression of a transgene in a mouse is unpredictable. (Paper No. 12, page 2.) This

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contention is premised on the Office's assertions that the phenotype of a transgenic mouse generally is (1) "dependent on the particular nucleotide sequence, operably linked to a specific promoter, encompassed within the transgene" that is placed into the transgenic mouse's genome and (2) dependent on "the site of integration of the transgene" in the mouse's genome. (*Id.*)

In response to these general arguments, applicants have presented more specific evidence pertaining to the presently claimed transgenic mice—evidence showing that the phenotype resulting from the expression of an oncogene under the control of a tissue-specific promoter in a transgenic mice is not unpredictable. That is one of skill in the art would reasonably predict that transgenic mice containing applicants' promoter sequence operatively linked to an oncogene would form tumors in the neurons where the transgene is expressed.

First, the specification demonstrates the creation of transgenic mice comprising applicants' promoter operably linked to a reporter gene that encodes a heterologous protein (β-galactosidase). In these transgenic mice, the heterologous protein, β-galactosidase, is expressed in neurons. Because applicants' promoter regulates expression of a reporter gene in a pattern that is characteristic of the normal expression pattern of the endogenous β2-subunit of the neuronal nicotinic acetylcholine receptor, no reason has been provided by the Office why one of skill in the art would not expect that applicants' promoter could be used in transgenic mice to regulate expression of other heterologous sequences, such as oncogenes, in a similar pattern.

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Second, applicants have provided prior art references[1] disclosing numerous examples of transgenic mice where sequences encoding oncogenic proteins were linked to various promoter and/or enhancer elements, resulting in tissue-specific expression and tumor formation. The major difference between these prior art transgenic mice and applicants' claimed transgenic mice is applicants' novel promoter sequence, which as discussed above, confers neuron-specific expression in transgenic mice. The teachings in these references have not been challenged by the Office and stand in contrast to the Office's assertion that expression would be unpredictable.

Thus, applicants have shown that the promoter sequence recited in the claims drives neuron-specific expression of a heterologous protein in a transgenic mouse. Applicants have also shown that prior to applicants' effective filing date, those skilled in the art had generated transgenic mice using various tissue-specific promoters to control the expression of different oncogenes, thereby resulting in a detectable phenotype—tumor formation.

Despite this showing, the Office continues to argue that "the art of transgenics is unpredictable with regard to transgene expression and a resulting phenotype." Paper No. 20, page 8. More specifically, the office asserts that "a phenotype resulting from expression of a transgene is dependent on the particular transgene, the level of transgene expression, and the site of integration." *Id.* at 6. Applicants acknowledge

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[1] **Kioussis**, *Oncogenisis and Transgenic Mice*, In: Grosveld, F. and Kollias, G. (eds.), Transgenic Animals, San Diego, CA, Academic Press, 1992: 195-210; and **Gordon**, *Transgenic Animals*, In: Bourne, GH, Jeon KW, Friedlander M (eds.), International Review of Cytology, San Diego, CA, Academic Press, 1989: 171-229.

that the site of transgene integration can affect the level of expression of the transgene in a transgenic mouse. But this fact does not render applicants' specification nonenabling. Rather, a skilled artisan can routinely screen the transgenic animals to determine those that express the transgene at a level sufficient to induce tumor formation.

The Office equates this routine screening "as welcoming trial and error experimentation to overcome the unpredictability of the transgenic art." Paper No. 20, page 6. In an analogous situation, however, the Federal Circuit has recognized that the amount of effort needed to screen hybridomas to find one with the desired properties is not excessive.

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practioners of this art are prepared to screen negative hybridomas to find one that makes the desired antibody.

In re Wands, 858 F.2d 7331, 740, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988) (reversing PTO's enablement rejection).

The same reasoning applies to the art of transgenic mice. As of applicants' filing date, skilled practioners were prepared to screen transgenic mice to find those that express the transgene at a level sufficient to induce tumor formation. Even assuming that this screening requires some experimentation, "the fact that some experimentation is necessary does not preclude enablement: what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus. Inc. v. Guardian Indus.*

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Corp., 75 F.3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996). Here, as in *Wands*, routine screening using well-known techniques does not require undue experimentation, particularly when considered in light of the other Wands factors. *See* M.P.E.P. § 2164.01(a).

The Office presented its own views regarding the Wands factors. According to the Office:

> A careful analysis of the Wands factors shows that 1) the **state of the transgenic art** is unpredictable with regard to the phenotype resulting from transgene expression; 2) the **claims are overly broad** with respect to polynucleotides encoding any oncogenic, immortalizing, or tumorigenic protein; 3) the instant specification has **failed to provide working examples** that correlate expression of any oncogenic, immortalizing, or tumorigenic protein with a particular phenotype; 4) the instant specification has **failed to provide guidance** for the creation of transgenic mice that express any oncogenic, immortalizing, or tumorigenic protein; and 5) that transgene expression is **unpredictable** at best.

Paper No. 20, pages 6-7 (emphasis in original).

Applicants do not agree with the Office's characterization of these factors and provide the following analysis, supported (where appropriate) by the evidence of record.

1. The State of the Prior Art

The Office asserts that the state of the transgenic art is unpredictable with regard to the phenotype resulting from transgene expression. Paper No. 20, page 6. In fact, however, the opposite is true. Kioussis discusses the development of transgenic mice

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expressing oncogenes under the control of transcriptional elements, including tissue-specific promoters. As explained by Kioussis:

> These constructs are introduced in the germ line of mice, and animals that carry these genes usually express the transoncogene in the tissue determined by the regulatory elements of the hybrid gene. This tissue often suffers a developmental disturbance and *in most cases* a tumour develops from the cells that express the oncogene.

Kioussis, p. 196 (emphasis added). Kioussis then lists examples of transgenic animals bearing an oncogene, including the SV40 large T antigen gene, the *myc* gene, a *ras*-activated gene, *neu*, and *fos*, under the control of a tissue-specific promoter. *Id.* And referring back to these earlier transgenic mouse examples, Kioussis observes that "the animals expressing a trans-oncogene in their tissues almost *invariably* develop tumours." *Id.* at 204 (emphasis added).

Gordon also discloses examples of transgenic mice, where sequences encoding oncogenic proteins were linked to various promoter and/or enhancer elements and expressed in specific tissues, causing tumor formation in the transgenic mice. Therefore, both Kioussis and Gordon demonstrate that one of skill in the art knew how to make and use transgenic mice expressing oncogenes under the control of tissue-specific promoters.

And according to Kioussis, tissue-specific expression of oncogenes in transgenic mice would "invariably," or at least "in most cases," lead to tumor formation, a

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recognized phenotype.[2] Thus, the prior art of record, including Kioussis and Gordon, refutes the Office's assertion that the state of the art of transgenics was unpredictable with respect to the phenotype resulting from the tissue-specific expression of oncogenes.

2. The Breadth of the Claims

The Office asserts that the claims are overly broad with respect to polynucleotides encoding any oncogenic, immortalizing, or tumorigenic protein. Paper No. 20, page 6. But the Office has not explained why one of skill in the art could not make and use the DNA sequence of the claimed invention using applicants' promoter sequence and a polynucleotide encoding an oncogenic protein. Moreover, the Office has focused on only one element of applicants' claimed invention, a polynucleotide encoding an oncogenic protein. According to the M.P.E.P., however, "[t]he examiner should determine what each claim recites and what the subject matter is when the claim is considered as a whole, not when the parts are analyzed individually." M.P.E.P. § 2164.08, 2100-186 (emphasis in original).

Applicants' claims define both the promoter and the nucleotide sequence encoding a polypeptide, which are present in the DNA sequences used for each of the processes (i.e., claims 46, 47, and 51-58), and which are present in each of the transgenic mice (i.e., claims 40-45 and 59-62), of the invention. In all of the claims, the promoter sequences used are "a promoter of the β2-subunit of the neuronal nicotinic

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2 "The Examiner agrees that tumor formation is a phenotype." Paper No. 20, page 8.

acetylcholine receptor having the sequence from about nucleotide -1125 to about nucleotide +38 of SEQ ID NO. 22." (*E.g.*, claim 40.) The specification demonstrates that this promoter sequence confers the expression pattern of the β2-subunit of the neuronal nicotinic acetylcholine receptor to the β-galactosidase protein in transgenic mice. Therefore, due to the recitation of this promoter sequence, the claims are not overly broad.

Having discovered this novel promoter sequence and demonstrated that it can drive neuron-specific expression of heterologous genes *in vivo*, applicants should be entitled to claim an embodiment of their invention encompassing transgenic mice, where the promoter sequence is operatively linked to a sequence encoding an oncogenic protein, as claimed. Such oncogenic sequences were well known the art, as shown, for example, in Kioussis or Gordon. Therefore, when the claims are viewed in their entirety, taking into account the recited promoter sequences, they are not particularly broad.

3. The Existence of Working Examples

The Office asserts that the instant specification has failed to provide working examples that correlate expression of any oncogenic, immortalizing, or tumorigenic protein with a particular phenotype. Paper No. 20, pages 6-7.

The specification is not devoid of relevant working examples. The specification demonstrates that the claimed promoter sequence drives neuron-specific expression of a heterologous protein, β-galactosidase, in a transgenic mouse. The difference

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between this working example and the claimed transgenic mouse is the replacement of the sequence encoding the β-galactosidase protein with a sequence encoding an oncogenic protein. It was well known in the art, however, that once an endogenous promoter was identified that could regulate the expression of a reporter gene in transgenic mice in a pattern that was characteristic of the expression pattern of the endogenous gene from which the promoter was derived, that promoter could be linked to a nucleotide sequence encoding a heterologous polypeptide, such as an oncogenic protein, to cause the heterologous polypeptide to be expressed in the cells or tissues of the mouse in which the endogenous gene from which the promoter was derived was normally expressed. (*See, e.g.,* Aguzzi et al.[3] and Camper et al.[4])

In addition, as discussed above, the prior art, including Kioussis and Gordon, demonstrate that expressing an oncogene in a transgenic mouse correlates with tumor formation, as claimed. Thus, in view of applicants' working examples and the level of skill in the art, one would expect the oncogenic sequence of applicants' claimed transgenic mice to be expressed in a pattern similar to that of the endogenous β2-subunit of neuronal nicotinic acetylcholine receptor and to lead to tumor formation in the neurons of these transgenic mice.

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[3] Aguzzi et al. has been discussed in further detail in applicants' previously filed Responses dated March 28, 2001, and August 30, 2001.

[4] Camper et al. has been discussed in further detail in applicants' previously filed Responses dated March 28, 2001, and August 30, 2001.

4. The Amount of Direction Provided by th Inventor

The Office asserts that the instant specification has failed to provide guidance for the creation of transgenic mice that express any oncogenic, immortalizing, or tumorigenic protein.

Again, this assertion appears to overlook the teachings of the specification. As discussed above, the application discloses a working example. The example shows that applicants created transgenic mice expressing the β-galactosidase gene under the control of the promoter of the of the β2-subunit of the neuronal nicotinic acetylcholine receptor. As noted above, the major difference between this working example and the claims is that the claims recite that the heterologous protein is an oncogenic protein—not β-galactosidase. But oncogenic proteins were well-known in the art (*see, e.g.*, Kioussis and Gordon). A patent need not teach and preferably omits what is well known in the art. *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); *see also*, M.P.E.P. § 2164.08 ("Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted.") Therefore, the specification provides significant guidance regarding the claimed invention.

5. The Level of Predictability in the Art

The Office asserts that transgene expression is unpredictable at best. For the reasons explained above, the prior art of record, including Kioussis and Gordon, establish that expression of oncogenes in transgenic mice predictably leads to tumor

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formation. Although transgene expression, in some cases, may not lead to tumor formation in the transgenic mouse[5], as discussed above, the skilled artisan could routinely screen the transgenic mice to identify those with the desired phenotype.

6. The Level of Skill in the Art

Although the Office did not address this factor, applicants note that the level of skill in the art of transgenic mice was high at the time of applicants' invention.

7. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

The Office also did not address this factor. As discussed above, however, the specification teaches how to make and use transgenic mice containing applicants' novel promoter sequence operatively linked to a sequence encoding a heterologous peptide. In the example, the heterologous protein is β-galactosidase. In the claims, the heterologous protein is an oncogenic protein. Accordingly, to practice the claimed invention, one of skill in the art need only substitute the disclosed β-galactosidase sequence with a sequence encoding an oncogenic protein and use routine screening methods to identify those transgenic mice that develop tumors.

Applicants respectfully submit that an analysis of these seven factors, based on the evidence as a whole, supports a finding that the specification, at the time the application was filed, taught one of skill in the art how to make and use the full scope of

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[5] Applicants note that the claims have been amended to recite "wherein the oncogenic protein is expressed at a level sufficient to induce tumor formation in said neurons." Therefore, the claims exclude mice that do not express the oncogenic proten at levels sufficient to induce tumor formation.

the claimed invention, without undue experimentation. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

The Examiner noted that claims 40-45 and 55-62 recite that the DNA sequence is introduced into a mouse at an embryonic stage. (Paper No. 20, pages 9-10.) According to the Examiner, introducing a heterologous DNA into multi-cell embryo would not give rise to a transgenic mouse all of whose germ cells and somatic cells contain the heterologous DNA, as recited in claims 40, 41, and 55. *Id.* at 10.

On the other hand, the Office noted that introducing a heterologous DNA into a fertilized oocye, which is a single cell, would be an appropriate technique for creating a transgenic mouse all of whose germ cells and somatic cells contain the heterologous DNA. *Id.* Accordingly, applicants have amended claims 40, 41, and 55 by deleting the reference in these claims to introducing the DNA sequence "at an embryonic stage."

The Examiner also asserted that "[t]he term embryonic stage does not accurately reflect the method of transgenesis used to produce the transgenic mice embraced by the claims particularly because the working examples provided on pages 35 and 38 of the specification discuss the creation of transgenic mice by microinjection of a reporter transgene into fertilized oocytes." *Id.* Applicants do not believe that it is proper to construe the claims by referring to the method applicants used for introducing a transgene into a transgenic mouse, as disclosed at pages 35 and 38 of the specification. Other methods for introducing transgenes into mice were known in the art at the time of applicants' effective filing date. For example, Aguzzi et al. discuss two

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most methods, microinjection of DNA into fertilized oocytes and embryonic stem cell transfer. Aguzzi et al., p. 4. Indeed, applicants used the latter gene transfer method to create transgenic knock-out mice that do not detectably express the β-2 subunit of the nicotinic acetylcholine receptor. Specification, pages 21-23.

Although claim 59 was amended by deleting the phrase, "wherein the DNA sequence was introduced into the first mouse at an embryonic stage," applicants note that claim 59 does not recite that all of the germ cells and somatic cells of the transgenic mouse contain the heterologous DNA sequence. Thus, claim 59 encompasses any transgenic mouse, regardless of how the transgene was initially introduced, so long as the oncogenic protein is expressed at a level sufficient to induce tumor formation.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office withdrew the previous rejections of claims 43 and 44 under 35 U.S.C. § 112, second paragraph. (Paper No. 20, page 11.) But the Office introduced several new grounds of rejection under 35 U.S.C. § 112, second paragraph, which are addressed below.

1. Claims 40, 41, 46, 55, and 59

The Office rejected claims 40, 41, 46, 55, and 59 under 35 U.S.C. § 112, second paragraph, as omnibus claims that are allegedly indefinite for referring to Figure 1. (*Id.* at 11-12.) Claims 40, 41, 55, and 59 have been amended and no longer refer to Figure 1. This amendment does not narrow the scope of claims 40, 41, 46, 55, and 59.

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2. Claims 40, 41, 46, 55, and 59

The Office rejected claims 40, 41, 46, 55, and 59 as allegedly lacking antecedent basis for the initial recitation of "the β2 subunit of neuronal nicotinic acetylcholine receptor." (*Id.* at 12.) Applicants have amended the claims to provide antecedent basis and respectfully request withdrawal of this rejection. This amendment does not narrow the scope of claims 40, 41, 46, 55, and 59.

3. Claim 41

The Office rejected claim 41 as allegedly lacking antecedent basis for the recitation "the germ cells" in line 2. (*Id.*) According to M.P.E.P. § 2173.05(e), "[i]nherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation 'the outer surface of said sphere' would not require an antecedent recitation that the sphere has an outer surface." Here, "the germ cells" are an inherent component of the claimed mouse. Just like the sphere has an outer surface, a mouse has germ cells. Thus, the recitation "the germ cells" does not lack antecedent basis. Applicants respectfully request that this rejection be withdrawn.

4. Claim 43

The Office rejected claim 43 as allegedly lacking antecedent basis for the recitation "the endogenous DNA of the second mouse" in lines 1-2 and "the endogenous DNA of the first mouse" in lines 2-3. (*Id.*) The endogenous DNA of the first and second

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mouse is an inherent component of the first and second mouse. Therefore, these recitations do not lack antecedent basis. M.P.E.P. § 2173.05(e). Applicants respectfully request that this rejection be withdrawn.

5. Claims 46 and 55

The Office rejected claims 46 and 55 as allegedly lacking antcedent basis for the recitation "the heterologous polypeptide" in lines 5-6 and line 7, respectively. (*Id.*) Claims 46 and 55 recite "a heterologous **protein**" at lines 1-2. Applicants have amended claims 46 and 55 (as well as claims 51, 56, and 60) to recite "a heterologous **polypeptide**" and respectfully request withdrawal of this rejection. This amendment does not narrow the scope of claims 46, 51, 55, 56, or 60.

Double Patenting Rejection

The Office provisionally rejected claim 40 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 15 of copending Application S.N. 08/465,712 (the '712 application). (Paper No. 20, page 13.) The '712 application issued as U.S. Patent No. 6,452,066 (the '066 patent) on September 17, 2002.

Applicants are filing a terminal disclaimer under the provisions of 37 C.F.R. § 1.321 to obviate the Examiner's obviousness-type double patenting rejection over claim 1 of the '066 patent.[6] The filing of a terminal disclaimer to obviate a rejection based on

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[6] Claim 1 of the '066 patent corresponds to claim 15 of the '712 application.

nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 874, 20 U.S.P.Q.2d 1392, 1394 (Fed. Cir. 1991). Applicants respectfully request that the Examiner withdraw this obviousness-type double patenting rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account no. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Date: December 13, 2002

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